The viral oncogene Np9 acts as a critical molecular switch for co-activating beta-catenin, ERK, Akt and Notch1 and promoting the growth of human leukemia stem/progenitor cells.

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Public Summary:
HERV-K (human endogenous retrovirus type K) type 1-encoded Np9 is a tumor-specific biomarker, but its oncogenic role and targets in human leukemia remain elusive. We first identified Np9 as a potent viral oncogene in human leukemia. Silencing of Np9 inhibited the growth of myeloid and lymphoblastic leukemic cells, whereas expression of Np9 significantly promoted the growth of leukemia cells in vitro and in vivo. Np9 not only activated ERK, AKT and Notch1 pathways but also upregulated beta-catenin essential for survival of leukemia stem cells. In human leukemia, Np9 protein level in leukemia patients was substantially higher than that in normal donors (56% vs 4.5%). Moreover, Np9 protein level was correlated with the number of leukemia stem/progenitor cells but not detected in normal CD34(+) hematopoietic stem cells. In addition, Np9-positive samples highly expressed leukemia-specific pol-env polyprotein, env and transmembrane proteins as well as viral particles. Thus, the viral oncogene Np9 is a critical molecular switch of multiple signaling pathways regulating the growth of leukemia stem/progenitor cells. These findings open a new perspective to understand the etiology of human common leukemia and provide a novel target for treating leukemia.

Scientific Abstract:
HERV-K (human endogenous retrovirus type K) type 1-encoded Np9 is a tumor-specific biomarker, but its oncogenic role and targets in human leukemia remain elusive. We first identified Np9 as a potent viral oncogene in human leukemia. Silencing of Np9 inhibited the growth of myeloid and lymphoblastic leukemic cells, whereas expression of Np9 significantly promoted the growth of leukemia cells in vitro and in vivo. Np9 not only activated ERK, AKT and Notch1 pathways but also upregulated beta-catenin essential for survival of leukemia stem cells. In human leukemia, Np9 protein level in leukemia patients was substantially higher than that in normal donors (56% vs 4.5%). Moreover, Np9 protein level was correlated with the number of leukemia stem/progenitor cells but not detected in normal CD34(+) hematopoietic stem cells. In addition, Np9-positive samples highly expressed leukemia-specific pol-env polyprotein, env and transmembrane proteins as well as viral particles. Thus, the viral oncogene Np9 is a critical molecular switch of multiple signaling pathways regulating the growth of leukemia stem/progenitor cells. These findings open a new perspective to understand the etiology of human common leukemia and provide a novel target for treating leukemia.